REMARKS

1. Traverse

The Office Action had required restriction among the pending claims and applicants had elected Group I with traverse. In support of the traverse, applicants had put forth a number of arguments specifically pointing out the reasons on which applicants based their conclusions that the requirement to restrict was in error. That those reasons were deemed unpersuasive should not serve as a basis for holding the response to the restriction requirement to have been made without traverse. Accordingly, applicants respectfully request that their election be acknowledged to have been made with traverse.

2. The Invention

The present invention relates to methods of screening for agents that may be useful in the treatment of cancer, as well as viral and microbial diseases. The screening methods of the present invention are designed to identify drugs that induce uracil misincorporation into DNA. In the context of cancer therapy, the significance of a rapid and sensitive method of identifying agents capable of inducing uracil misincorporation into DNA lies in the fact that current anticancer drugs have a notoriously low response rate, necessitating the administration of high doses that are often toxic to the cancer patient. In addition, anticancer drugs frequently lose their effectiveness because cancer cells rapidly acquire resistance by a variety of mechanisms. One such known mechanism of drug resistance in cancer cells, particularly with respect to chemotherapeutics that target the thymidylate synthase pathway, is through the upregulation of dUTPase activity. Because increased dUTPase activity protects cancer cells from the lethal effects of uracil misincorporation into DNA, the identification of agents that specifically interfere with this protective response of

cancer cells against current anticancer drugs is an urgent priority. The present invention provides modified strains of cells that allow for the rapid identification of such agents by their precise mechanism of action, including the activation of distinct cell cycle checkpoints, thereby eliminating false positive results which would require additional time-consuming experimentation in most other assays.

3. The Invention Is Not Obvious Under 35 U.S.C. §103

Claims 1-10 have been rejected under 35 U.S.C. §103(a) over Goulian et al. (PNAS Vol. 77 No. 4, pp. 1956-1960, 1980) in view of Gadsden et al. (EMBO, Vol. 12, No. 11, pp. 4425-4431, 1993). The basic requirements of a prima facie case of obviousness are set forth in MPEP 2142:

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, **the prior art reference (or references when combined) must teach or suggest all the claim limitations**. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Thus, the claims under consideration must be considered with all their limitations. Claim 1 is the only independent claim under consideration in the instant application. Claims 2-10 depend from claim 1 and introduce additional limitations. Claim 1 reads as follows:

> 1. A method for determining if a test compound induces uracil misincorporation into DNA, the method

comprising:

a) providing aliquots of the following cells:

i) wildtype cells

ii) **cells overexpressing dUTPase;**

iii) **cells overexpressing a uracil-DNA glycosylase**; and

iv) cells expressing the uracil-DNA glycosylase inhibitor protein Ugi or cells possessing a compromised uracil-DNA glycosylase function;

b) exposing the cells to an agent that directly or indirectly inhibits thymidylate metabolism, in the presence or absence of the test compound;

c) measuring one or more features of the exposed cells, the features comprising:

i) cell growth or viability

ii) cell cycle checkpoint arrest;

iii) presence of replication intermediates in the cells;

iv) amount of dUTP present in the cells; and

v) presence or amount of uracil in DNA of the cells; and

d) interpreting the measured features, wherein a profile in the four cell types which is indicative that the test compound induces uracil mis-incorporation into DNA comprises one or more features in each of the cell types comprising:

i) in the wildtype cells, cytotoxicity, cell cycle arrest at G1/S or early S phase, presence of replication intermediates, elevated dUTP pools or little or no detectable uracil in the DNA;

ii) in the dUTPase overexpressing cells, enhanced resistance to cytotoxicity, cell cycle arrest at mid S-phase, presence of replication intermediates, low dUTP pools, or little to no detectable uracil in DNA.

iii) in the uracil-DNA glycosylase overexpressing cells, cytotoxicity or enhanced cytotoxicity, cell cycle arrest at G1/S or early S-phase, presence of replication intermediates, elevated dUTP pools, or little to no detectable uracil in DNA; and

iv) in the nonfunctional uracil-DNA glycosylase cells, enhanced resistance to cytotoxicity, cell cycle arrest at G2/M phase, reduced presence of replication intermediates, elevated dUTP pools, or stable uracil incorporation into DNA.

The Office Action correctly ascertained that Goulian et al. do not teach cells overexpressing dUTPase or uracil-DNA glycosylase or uracil-DNA glycosylase inhibitor protein. (Office Action page 4, lines 8-9). However, the Office Action asserted that

> "...Gadsden et al. disclose a method comprising **dUTPase expressing cells (EM932), uracil-DNA glycosylase (dut⁻) expressing cells** and uracil glycosylase inhibiting cells (tup⁻)."

(Office Action page 4, lines 12-13)

Applicants respectfully submit that neither Gadsden nor Goulian teach or suggest providing aliquots of cells **overexpressing dUTPase** and cells **overexpressing uracil-DNA glycosylase**. Overexpression of a protein requires levels of the particular protein that are in excess of those produced in normal, or wild-type, cells and should thus be distinguished from the term "expressing" that denotes normal, or wild-type levels of expression. The EM932 yeast transformants in Gadsden et al., referred to in the Office Action as "dUTPase expressing cells," are cells that do not express dUTPase at all. Instead, these cells are derivatives of the uracil glycosylase-deficient strain PY32 in which the DUT1 (dUTPase) gene was disrupted, leading to no expression of dUTPase, and in which the uracil glycosylase deficiency was restored by a plasmid carrying the wild-type uracil glycosylase gene (UNG1). Further, the "uracil-glycosylase expressing cells" referred to as "dut⁻" by the Office Action are in fact dUTPase null mutants that exhibit no dUTPase activity. According to the teachings of Gadsden et al.these dUTPase null mutants are either be wild-type for dUTPase (dut⁻ Ung⁺; EM932) or dUTPase-deficient (dut⁻ ung⁻; EM931). Nowhere however do Gadsden or Goulian disclose or suggest overexpressing dUTPase or uracil-glycosylase or providing cells that overexpress dUTPase or uracil-glycosylase. Nor do Gadsden, Goulian, the teachings of the prior art, or the knowledge of

a person skilled in the art contain any suggestion or provide any motivation to modify or combine the teachings of Gadsden et al. and Goulian et al. in a manner that would result in the invention as claimed by applicants, including providing aliquots of cells overexpressing dUTPase and cells overexpressing uracil-DNA glycosylase.

Because the Gadsden and Goulian references, even when combined, do not teach or suggest all the claimed limitations of the present invention, applicants' invention, as claimed, could not have been obvious to a person of skill in the art. Applicants respectfully note that because independent claim 1 is nonobvious under 35 U.S.C. 103, dependent claims 2-10 are also nonobvious. (MPEP 2143.03). Accordingly, applicants respectfully request that the rejection of claims 1-10 under 35 U.S.C. § 103(a) be withdrawn. Applicants believe that the invention as described and claimed is patentable and thus an early allowance is earnestly sought.

Respectfully submitted,
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